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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/218,660	12/22/1998	EVAN C. UNGER	UNGR-1520	2775

7590

07/03/2003

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EXAMINER

SHARAREH, SHAHNAM J

ART UNIT

PAPER NUMBER

1617

DATE MAILED: 07/03/2003

37

Please find below and/or attached an Office communication concerning this application or proceeding.

**Advisory Action**

Applicati n No.

09/218,660

Applicant(s)

UNGER ET AL.

Examiner

Shahnam Sharareh

Art Unit

1617

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 21 April 2003 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

**PERIOD FOR REPLY [check either a) or b)]**

- a) ☒ The period for reply expires 5 months from the mailing date of the final rejection.
- b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☒ A Notice of Appeal was filed on 21 April 2003. Appellant's Brief must be filed within the period set forth in ~~37-CFR-1.192(a)~~, or any extension thereof (~~37-CFR-1.191(d)~~), to avoid dismissal of the appeal.
2. ☐ The proposed amendment(s) will not be entered because:
- (a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);
- (b) ☐ they raise the issue of new matter (see Note below);
- (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
- (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: \_\_\_\_\_

3. ☐ Applicant's reply has overcome the following rejection(s): \_\_\_\_\_.
4. ☐ Newly proposed or amended claim(s) \_\_\_\_\_ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
5. ☒ The a) ☐ affidavit, b) ☐ exhibit, or c) ☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.
7. ☒ For purposes of Appeal, the proposed amendment(s) a) ☒ will not be entered or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: \_\_\_\_\_.

Claim(s) objected to: \_\_\_\_\_.

Claim(s) rejected: 100-103, 127, 194-200, 203, 210-228, 294-300, 303, 310-329, 331-337, 347-356.

Claim(s) withdrawn from consideration: \_\_\_\_\_.

8. ☐ The proposed drawing correction filed on \_\_\_\_\_ is a) ☐ approved or b) ☐ disapproved by the Examiner.
9. ☐ Note the attached Information Disclosure Statement(s) (PTO-1449) Paper No(s). \_\_\_\_\_.
10. ☐ Other: \_\_\_\_\_

  
RUSSELL TRAVERS  
PRIMARY EXAMINER  
GROUP 1200

Continuation of 5. does NOT place the application in condition for allowance because: of the reasons of record. With respect to the rejection of claims under 35 USC 103 (a) over Grinstaff, In view of Wallach, Allen and Ginsberg, Applicant argues that Grinstaff explicitly uses "substantially cross-linked" phospholipids. Applicant construed this teaching of Grinstaff to mean "more than 50% crosslinking." (See Reply After Final, Paper No. 35 at page 3). Applicant relies on the Merriam-Webster's Collegiate Dictionary, 12<sup>th</sup> edition to support such argument. Accordingly, Applicant argues that the instant claims are distinguishable over Grinstaff because they are less than about 50% crosslinked. (see Reply After Final at pages 4-5).

In response, Examiner states that as the initial matter, "substantially" is defined in Webster's II New Riverside University Dictionary as "being of considerable importance, value, degree, amount or extent." Accordingly, Webster's II provides an alternative meaning to the term "substantially." Contrary to Applicant's interpretation, Examiner views such term to be directed to a considerable amount. The term "considerable" is respectively defined as "worthy of consideration," which subsequently reflects on the term "substantially" to mean "an amount worthy of consideration." Accordingly, Examiner views this limitation to reflect the degree of importance of the cross-linking in Grinstaff's shell, and not a measurement of quantity of crosslinking. Therefore, any amount that leads to the desired properties of Grinstaff's shells can qualify as providing "substantially crosslinking." This amount can be 40% or 99% depending on the type of polymerized phospholipid employed. Thus, Applicant's conclusion that at least 50% or more of Grinstaff's shells must be crosslinked is not persuasive, because there is no literal or scientific support for such conclusion.

Second, Applicant has not provided any evidence of unexpected results. The rejection in question is made over an obviousness type analysis. Accordingly, the primary reference, Grinstaff, provides for polymeric shells containing biocompatible materials that are substantially crosslinked and further is modified by suitable agent such as phospholipid (see claim 1, and claim 26). The arguments presented acquire to the fact that the only difference between the vesicle of Grinstaff and the instant vesicle is in the degree of polymeric crosslinking. Thus, the differences between the instant vesicles and those of Grinstaff appear to be in degree not in kind. However, no evidence is provided to indicate unexpected results when the degree of polymeric crosslinking, for example, is modified from 51% (Grinstaff's shell) to 49% (the scope of the instant vesicles). It is well established that when the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation (See MPEP 2144.05 II).

Accordingly, Grinstaff's shell are within the scope of the instant vesicles unless it is shown that a lower degree of polymerization, as instantly claimed, provides an unexpected results. Thus, claims stand rejected.

Applicant's arguments with respect to the rejected claims over Wallach, Allen in view of Schneider, Porter and Ginsberg, have been fully considered but are not found persuasive. Applicant primarily argues that Schneider is not directed to gas filled vesicles, or gaseous liposomes, rather microbubbles (Reply After Final at page 7-8). In response, Examiner first draws applicant's attention to the scope of the instant claims. The instant claims are directed to formulations comprising gas-filled vesicles which comprise one or more membranes encapsulating an internal void that contains a gas, said membrane comprising a phospholipid and being substantially free of crosslinked protein and polymers. As the initial matter, the pending generic claims are directed to vesicles which encompasses microbubbles. (see instant specification, page 13, lines 4-5). Accordingly, not only a microbubble but anything the like microbubbles are encompassed by the term vesicles. The vesicles taught in Schneider are by no means excluded from the scope of the instant claims, because they contain at least a lamellar surfactant surrounding the bubbles and further entrap a gas (see Schneider col 7, lines 55-67; col 9, lines 1-3). Moreover, the bubbles of Schneider, even if not in the traditional spherical form, are contained within a barrier as they are bound by a lamellar surfactant. Such teachings meet the requirement of the walls within the instant vesicles. Furthermore, Applicant's arguments essentially ignores the general knowledge in the art as provided by Schneider. Specifically, Schneider revisits Ryan's invention for comparative purposes. Ryan's comparative liposomes are clearly gaseous liposomes within the scope of the pending claims. Thus, the notion of gaseous microbubbles or liposomes are well established in the art. Finally, Schneider is not used as a primary reference in the instant rejection, rather as a secondary reference complementing Wallach's teachings. Wallach provides for encapsulating targeted lipid vesicles containing a drug. Schneider merely provides a teachings that such delivery vesicles can contain gas for diagnostic or therapeutic purposes. Unlike, In Re Wesslau, both the primary and secondary reference complement each other here. Wallach teaches that his vesicles can encapsulate various therapeutic and diagnostic agents. Schneider teaches that gas can be one of such agents. In Wesslau, the essential inventive step was not foreseen by the combined references. Here it has, because all elements are taught by the combined references. Therefore, the rejection does not employ improper pick and choose from any one reference. Rather, it sets forth motivation for showing a prima facie obviousness. Accordingly, the rejection is proper for the reasons of record.